Epidemiology, Pathophysiology and Contemporary Management of Cardiogenic Shock - A position statement from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).

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Abstract:

Cardiogenic Shock (CS) is a complex multifactorial clinical syndrome with extremely high mortality, developing as a continuum, and progressing from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. There is a large spectrum of CS presentations resulting from the interaction between an acute cardiac insult and a patient's underlying cardiac and overall medical condition. Phenotyping patients with CS may have clinical impact on management because classification would support initiation of appropriate therapies. CS management should consider appropriate organization of the healthcare services, and therapies must be given to the appropriately selected patients, in a timely manner, whilst avoiding iatrogenic harm. Although several consensus-driven algorithms have been proposed, CS management remains challenging and substantial investments in research and development have not yielded proof of efficacy and safety for most of the therapies tested, and outcome in this condition remains poor. Future studies should consider the identification of the new pathophysiological targets and high-quality translational research should facilitate incorporation of more targeted interventions in clinical research protocols, aimed to improve individual patient outcomes. Designing outcome clinical tri-

als in CS remains particularly challenging in this critical and very costly scenario in cardiology, but information from these trials is imperiously needed to better inform the guidelines and clinical practice.

The goal of this review is to summarize the current knowledge concerning the definition, epidemiology, underlying causes, pathophysiology and management of CS based on important lessons from clinical trials and registries, with focus on improving in-hospital management.

Key words: Cardiogenic Shock, Definition, Mechanical Circulatory Support,

Introduction

Cardiogenic shock (CS) represents the most severe form of acute heart failure (AHF) syndromes. Although there is no uniform definition of CS (1-8), CS is a low cardiac output (CO) state primarily due to a cardiac dysfunction, leading to severe end-organ hypoperfusion associated to tissue hypoxia and increased lactate levels. This pathophysiology frequently leads to multi-organ failure and death.

Although recent guidelines (4) describe a singular CS presentation as part of AHF Syndromes, there is a large spectrum of CS phenotypes (2, 3, 6) resulting from the interaction between a cardiac insult and a patient's underlying cardiac and overall medical condition (9). While the initial presentation of the patients with CS may appear similar, reflecting the systemic effects of an initial acute reduction in CO, frequently the patient condition rapidly changes and evolves into several clinical phenotypes through distinct mechanisms determined by the underlying etiology and severity of the primary cardiac insult. Cardiac insult causing severe impairment of cardiac per-

formance may be acute, as result of the acute loss of myocardial tissue (AMI, myocarditis) or may be progressive as seen in patients with chronic decompensated HF who experienced a decline in disease stability as result of severe precipitants, iatrogenic factors, poor adherence to guideline-based therapies, factors triggering an acute worsening of their chronic disease.

Despite advanced management, including etiological treatment (10) and mechanical circulatory support (MCS) (10-12), CS represents the most severe manifestation of AHF with in-hospital mortality between 30-50%, depending on underlying etiology (1).

The goal of this review is to summarize the current knowledge concerning the definition, epidemiology, underlying causes, pathophysiology and management, based on important lessons from clinical trials and registries, with focus on improving in-hospital management.

Definition and Classifications

Based on clinical criteria, diagnosis of CS mandates presence of clinical signs of hypoperfusion, such as, cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. In addition, biochemical manifestations of hypoperfusion, elevated creatinine, metabolic acidosis and elevated serum lactate, are present and reflect tissue hypoxia and alterations of cellular metabolism, potentially leading to organ dysfunction. CS is a clinical diagnosis (4,7) and hemodynamic parameters, such as reduced cardiac index (CI) and elevated pulmonary capillary wedge pressure (PCWP) are not mandatory in clinical practice.

Although, recent ESC-HF Guidelines (4) and many CS definitions (1, 3, 6) include hypotension defined as systolic blood pressure (SBP) <90 mmHg for more than 30

min, or the need of catecholamines to maintain SBP >90 mmHg, it is well-recognized that in shock, compensatory mechanisms may preserve blood pressure through vasoconstriction, while tissue perfusion and oxygenation may be significantly decreased. Thus, hypoperfusion is not always accompanied by hypotension and hypotension without hypoperfusion may portend a better prognosis (2, 5, 8). In the SHOCK registry, clinical signs of hypoperfusion were associated with a substantial risk of in-hospital mortality even in normotensive patients, suggesting that early recognition of hypoperfusion signs, identifies "high-risk" patients regardless of hypotension (2). The Task Force of the European Society of Intensive Care Medicine defined shock (including its subtypes) as a "life-threatening, generalized form of acute circulatory failure associated with inadequacy of tissue perfusion to provide enough oxygen to sustain basal metabolism at cellular level", where the presence of low SBP was not a prerequisite for defining CS (13). Based on these considerations, we propose to define CS as a syndrome caused by a primary cardiovascular disorder in which inadequate CO results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia, which depending on its severity, may result in multi-organ dysfunction and death.

CS registries (14) and consensus documents (7, 15-17) described a large phenotypic variability of CS, as result of the diverse aetiologies, pathogenetic mechanisms, hemodynamics and stages of severity. CS may arise in advanced chronic HF when acute precipitants trigger decompensation or may manifest as an acute onset, *de novo* presentation, most often caused by ACS. Categorization according to the underlying aetiology, ACS-vs non-ACS-related, aims to early guide management strategies towards underlying cause. Also, the presence/absence of previous cardiac arrest (CA),

is important as phenotypes differ significantly in terms of priorities for initial management and also outcomes.

Based on clinical severity and response to treatment, the spectrum of CS can be divided into pre-CS, CS, and refractory CS (15) (**Figure 1**). Early identification of CS allows rapid initiation of appropriate interventions to reverse the underlying cause and introduction of supportive therapies. The presence of clinical signs of peripheral hypoperfusion even with preserved SBP, is referred as "pre-shock" (15) and precedes overt CS. Pre-shock may occur in severe AHF which can also be associated with clinical signs of tissue hypoperfusion but without compromising cellular basal metabolism and having normal lactate (2, 7, 15). This state should be differentiated from "Normotensive CS" which represents an entity of CS with all features of hypoperfusion and cellular alterations (including cellular hypoxia and elevated lactate) but without hypotension. Patients with normotensive CS have a greater systemic vascular resistance, but similar left ventricular ejection fraction, cardiac output, and pulmonary capillary wedge pressure, as patients with classic CS, thus highlighting the risk of hypoperfusion (2,7).

At the end of the spectrum of severity, refractory CS has been defined as CS with ongoing evidence of tissue hypoperfusion despite administration of adequate doses of 2 vasoactive medications and treatment of the underlying etiology (15, 18).

The recently published Society for Cardiovascular Angiography and Interventions (SCAI) (16) describes five evolutive stages of CS, from A (at risk of CS) to E (extremis) (**Figure 1**) including a modifier for cardiac arrest (CA). This classification can be applied rapidly bedside upon patient presentation, across all clinical settings. The SCAI classification utilizes bedside clinical assessment of hypoperfusion, measure-

ment of lactate level and invasive hemodynamic evaluation. Recently, the SCAI classification has been validated in a large cohort of unselected CICU patients and SCAI classification provided robust mortality risk stratification regardless aetiology of CS, in a manner that was amplified by the presence of CA (19). The strong association between SCAI shock stages and mortality in a heterogeneous CICU population, even after adjustment for known predictors of mortality, emphasizes the robustness of this classification system.

In the SHOCK trial (1), CS definition required hemodynamic parameters, such as reduced cardiac index (CI <2.2L/min/m^2) and elevated pulmonary capillary wedge pressure (PCWP >15mmHg). However, this definition reflects only "left-sided" CS, but there are diverse hemodynamic phenotypes for CS (7) determined by the association of the systemic inflammatory response syndrome (SIRS) (20, 21) and by the type of cardiac involvement (left vs right) (22) . The common physiological characteristic is low CI, but PCWP, central venous pressure (CVP) and systemic vascular resistance (SVR) may vary (7) (**Figure 1**).

Epidemiology and Prognosis

The prevalence of CS varies according to the definition of CS, clinical settings care and era of data collection. CS accounts for 2-5% of AHF presentations (5, 10, 23-27), with a prevalence in ICU/ICCU datasets of 14-16% (10, 28). In-hospital mortality varied between 30 and 60% (23-27), with nearly half of in-hospital deaths occurring within the first 24 hours of presentation (5). One-year mortality is approximately 50-60% (29), with 70-80% of deaths occurring in the first 30 to 60-days after onset of CS

(29-31) suggesting that the risk of death is time-dependent and clustered in the early post-discharge period.

The incidence of CS complicating ACS is 4-12%, with 30-40% of cases occurring at admission (32-34), and 60-70% occurring in the course of hospitalization. However, in a French registry enrolling 10 000 consecutive AMI patients over 10 years, the prevalence of CS following AMI decreased from 5.9% in 2005 to 2.8% in 2015 (35). Overall, in-hospital mortality of CS complicating AMI has remained unchanged in the last 10 years at 40-50% (32, 36-39), with higher rates being reported in CS developing during hospitalization (34). However, recent US datasets reported lower mortality rates of 36.5% (40) and 38.8% (41).

A decade ago, 81% of CS was due to underlying ACS (42), however, the contribution of ACS has declined over the past 2 decades (43), in parallel with an increase of CS of other aetiologies (10). In a large US registry including 144,254 patients with CS of any aetiology, the proportion of ACS-CS has fallen between 2005 and 2014 from 65.3% to 45.6% (10). Also, in a contemporary ICCU dataset in the US and Canada, only a third of CS were related to ACS, while the remainder comprised ischemic cardiomyopathy without ACS (18%), nonischemic cardiomyopathy (28%) and other causes (e.g. incessant ventricular tachycardia, severe valve disease) in 17% (28). NonACS-CS patients are more resource-intensive and have a greater burden of disease (more severe pre-existent HF, pulmonary hypertension, arrhythmias), but in-hospital survival is significantly better than ACS-related CS (28, 42). In CardShock (42), ACS has been shown to be a predictor of worse outcomes in patients with CS (OR 7.4, 95% CI 1.9–29.8).

Patients with ACS and CS have an acute and irreversible loss of myocardial tissue of significant magnitude which often triggers inflammatory and other systemic responses. This is in the contrast to the reversible nature of cardiac dysfunction seen in other aetiologies of CS. Secondly, patients with CS complicating AMI are older, with higher rates of cardiac arrest, diabetes, peripheral vascular disease and ischemic stroke, that contribute to worse outcome compared to non AMI CS (28, 40, 42). Despite an overall higher rate of revascularization over time, AMI-CS patients with greater comorbidity still/consistently underwent less coronary angiography and revascularization (43,44).

CS is a more common complication of ST-elevation myocardial infarction (STEMI) than non-STEMI (NSTEMI), with STEMI being more likely to present with CS on admission versus developing after hospitalization in NSTEMI (10, 45). Although, initial reports (46) suggested worse early mortality for NSTEMI vs STEMI, this has not been supported by later data (29).

Pathophysiology of CS

Although aetiologies vary widely (15, 18, 47) (**Table 1**), the pathophysiology of CS comprises several unique yet overlapping components to be considered : an initial cardiac insult that decreases CO, central hemodynamic alterations (including changes in the relation between pressure and volume with increase in LV and RV filling pressures), microcirculatory dysfunction, a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction (**Figure 2).** Although these mechanisms might be considered as temporal stages of CS, each may occur simultaneously, the magnitude of the initial cardiac insult and/or early application of interventions may either mask or delay some of these stages (48).

Furthermore, precipitating factors (49-51), may cause an acute deterioration of cardiac compensation evolving to CS, and worse outcomes were described in the patients with non-cardiovascular precipitating factors, such as infection.

Severe LV failure secondary to loss of the myocardial tissue after a large AMI represents the classical pathogenic mechanism of CS. In addition to the acute loss of myocardial tissue, mechanical complications of AMI, acutely alter loading conditions leading to acute LV and RV dysfunction. Distinct to ACS, CS can result as a consequence of a severely reduced CO due to primary cardiac, valvular, electrical, or pericardial abnormalities. RV dysfunction, either by primary contractile dysfunction or secondary or secondary preload/afterload mismatch, may be exclusively responsible of CS (e.g. acute PE, isolated severe primary TR, RV cardiomyopathies) or may contribute to CS in association with left-sided pathologies (e.g. RV infarction associated to inferior wall MI, severe PHT in setting of valvular disease, post cardiac surgery or LVAD implant). CS in setting of RV dysfunction may manifest with or without pulmonary hypertension (**Table 1**). Other conditions, including severe valvular disease, tamponade, acute myocarditis, left ventricular outflow obstruction in Takotsubo Syndrome, postpartum cardiomyopathy, cancers, arrythmias, and post-cardiotomy syndrome, may destabilize and complicate with CS.

As a consequence of an acute decrease of LV contractility, CO, stroke volume (SV) are reduced leading to an acute reduction of blood pressure (BP), and corresponding elevation of LV end-diastolic pressure (15). As a reaction to the BP drop, compensatory vasoconstriction occurs (including venoconstriction which functionally shifts blood volume into the circulating compartment, causing elevations of central venous and pulmonary venous pressures), altering ventricular-arterial coupling (15). Low cardiac power output (CPO) (CO x BP), an indicator of significant LV dysfunc-

tion, has proven to be a strong hemodynamic predictor of poor outcome at CPO<0.53W (52). In terms of monitoring and prognosis, CPO is superior to SBP measurements in CS. SBP can be increased with use of high-dose inotropes/vasopressors, but at the expense of marked increase in peripheral resistance. The calculated pulmonary artery pulsatility index (PAPi) <0.9 can identify significant RV failure (53).

Microcirculatory dysfunction is present early in CS patients and may precede central hemodynamic abnormalities (48). It is associated with the development of multi-organ failure and predicts poor outcome in patients with CS complicating AMI (54). As the microcirculatory network is flow dependent, the decrease in CO and elevated vascular tone probably reduces capillary responsiveness discordant to the cellular metabolic requirements resulting in cellular hypoxia (55). However, even in severe hypoxia, mitochondrial viability and function are preserved for several hours (56), and animal models suggest an initial up-regulation of mitochondrial function in order to match metabolic demand (57). In a sub-analysis of the CULPRIT-SHOCK trial, there was a significant and independent association between the microcirculatory perfusion parameters and the combined clinical endpoint of 30-day all-cause death and renal replacement therapy, especially in patients with loss of hemodynamic coherence between microcirculation and macrocirculation (58). Although targeting the microcirculation in CS is appealing (59), the response of the microcirculation to therapeutic interventions is often dissociated from systemic effects (60) and interventions aimed at normalization of the microcirculation in CS have proved inconclusive.

Clinically overt inflammation is seen in 20-40% of CS patients by day 2 post-CS onset, and may result in an initially low SVR (21). Increased levels of cytokines (interleukin-1β, 6, 7, 8 and 10) have been detected shortly after CS onset, with levels corre-

lating with early mortality (61). Local factors, such as NO-mediated pathological vasodilatation, dysglycemia and acute increase of advanced glycation end-products further induce vasodilation, and are associated with increased mortality (62) (63). In addition, infection complicates approximately 20-30% of CS cases (64). Risks for bloodstream infection include vascular access as well as hypoperfusion-related damage to the gastrointestinal mucosal barrier and resulting bacterial translocation.

Multi-organ dysfunction is the result of both macro-hemodynamic alterations (65) and microcirculatory dysfunction (66) and portends a poor prognosis. The gut appears to be among the first organs involved in shock, and microcirculatory injury in the intestinal barrier leads to increased bacterial translocation (67, 68). Lipopolysaccharide or endotoxins produced by gram negative bacteria enter the circulatory system and contribute to cytokine generation and inflammation (68). In a recent retrospective analysis, including 443 253 patients with AMI-CS (51), there was a gradual relationship between the number of dysfunctional organs and in-hospital mortality, a lower probability of home discharge and higher in-hospital cost.

Proteonomic research may further assist the understanding of pathophysiology, improves risk-stratification and provides an opportunity for treatment (69). A recent research study identified a complex of 4 proteins (CS4P) associated to multiorgan dysfunction, systemic inflammation and immune activation (69). During the early hours of CS, changes in the expression of CS4P may precede overt multiorgan failure and identify patients at a higher mortality risk (69).

Further, intra-plasmatic Dipeptidyl-peptidase-3 (DPP-3) was associated to worsening hemodynamics, evolution to refractory CS and 90-day mortality (70, 71). DPP-3 is a cytosolic enzyme associated with alteration in inflammation pathway, inducing strong

negative inotropic and vasodilation effect (71) which can be reversed in animal models (69, 70).

Iatrogenic factors, such as administration of countershocks, cardio-depressant sedatives (such as propofol), antiarrhythmics, beta-blockers, excessive use of diuretics, excessive volume loading in RV shock, could further contribute to the cardiovascular dysfunction in CS (45, 72).

In-hospital monitoring and investigations

Immediate assessment of hypoperfusion signs and continuous monitoring of SBP, rhythm, respiratory rate and saturation are recommended (I/C) (4, 73) (*Supplementary Table)*. In addition to SBP, pulse pressure (PP) should be closely monitored especially in patients with Normotensive CS. A SBP ≥90 mmHg or mean arterial pressure (MAP) in the range of 60–65 mmHg is generally recommended, but this target BP has not been validated in RCTs (4).

A *12 lead ECG* should be immediately performed (I/B) followed by continuous ECG monitoring.

Echocardiography should be used to determine the underlying diagnosis, guide interventions and monitor response to therapies (**Figure 3**), and should be performed urgently, ideally with an immediate, comprehensive study undertaken by an expert (75). Where not available, Focused Cardiac UltraSound (FoCUS) (76) can provide useful information, and should be followed by echocardiography as soon as possible (77).

In CS, echocardiography has a central role to identify potential underlying causes and associated pathophysiology because without identification and treatment of the under-

lying cause, the outcome is usually fatal. Standard echocardiographic evaluation should provide rapidly sufficient information to confirm/exclude tamponade, mechanical complications of AMI, LVOTO, severe valvular lesion. Concomitant assessment of LV and RV function, and estimation of the left and right filling pressures should be also included in Echo protocols. In ED, lung ultrasound (LUS) provides point-of-care evaluation of pulmonary congestion, lung consolidation, pleural effusion, and pneumothorax (76).

The non-invasive methods of hemodynamic monitoring (78) have certain advantages though none have been adequately validated in the context of CS and should not be used solely.

Chest X-ray remains important for the evaluation of congestion and to monitor the catheter and cardiac device position (73).

Invasive monitoring using *an arterial line* is recommended in all CS patients (I/C recommendation) (4).

We recommend insertion of a *central venous catheter* in all patients with CS (5, 8), allowing transduction of central venous pressure, and measurement of $ScVO^2$, and access for vasoactive drug administration (79).

The routine use of a pulmonary artery catheter (PAC) remains contentious. The ESCAPE trial (80) and several studies (81-85) suggested no overall benefit in terms of mortality or readmissions from routine invasive assessment of hemodynamics compared to rigorous clinical assessment and a high rate of catheter-related complications. Although, the majority of PAC studies, including ESCAPE, didn't enroll CS patients, the use of PAC has decreased significantly over the past decade and is specially reserved for the care of critically ill patients in tertiary hospitals (86) with high level of

user competence. In a recent retrospective study including 915,416 patients with CS, mortality in patients with CS and PAC has improved over time compared with those without PAC, which may reflect better selection of patients or better use of information to guide therapies (41). In an US registry including 15 259 CS-AMI patients supported by Impella device, the use of PAC for hemodynamic monitoring was associated with higher survival (87).

Based on expert opinion, PAC is currently recommended in selected patients who failed to respond to initial therapeutic interventions (persistence of hypotension and hypoperfusion) (IIb/C) (4, 73), or in case of diagnostic/therapeutic uncertainty (cases of mixed shock or patients with advanced right HF) (13).

Biomarker use can provide information for the recognition, prognostication and management of CS. Elevated lactate reflects inadequate tissue oxygenation/metabolism, and the diagnosis of shock includes serum lactate >2 mmol/ (4), which also have a strong prognostic role (13, 88). Lactate levels may be used in conjunction with hemodynamic data, and in NCSI dataset, stratifying CS patients according to CPO (> or <0.6 W) and lactate (> or <4 mg/dL) at 12–24 h was the best predictor of survival (74).

Potential causes of lactate elevations, such as, diabetic ketoacidosis, liver insufficiency, trauma, epinephrine, propofol, linezolid, should be considered when lactate level is dissociated to hypoperfusion status (89). Although lactate clearance is a signal of response to interventions, improved organ function and survival (90, 91), due to the long-time delay between the intervention and drop in lactate, lactate targeted management has not been associated to clinical benefit (13). Natriuretic peptides (NPs) are markers of disease severity and indicative of increased filling pressures. While a

retrospective analysis suggested elevated NP were predictive for development of CS (92), this has not been prospectively validated.

Current guidelines recommend at least daily monitoring of complete blood count, serum electrolytes, serum creatinine, liver function tests, coagulation, serial cardiac troponin levels, lactate, arterial blood gas analysis and mixed venous oxygen saturation (when PAC available) (7, 73).

Risk stratification and prognostic models

Current CS risk scores developed in the post-PCI era (*Supplementary Table 1)* relate to identification of patients at risk for developing CS (ORBI-score) (93), prediction of short-term mortality (CardShock, IABP-SHOCK-II) (42, 94) and prediction of survival after the use of MCS (ENCOURAGE, SAVE-ECMO) (95-97). The CardShock score predicts mortality in CS with a large spectrum of etiologies, while the rest address only AMI-CS patients. The only scores with external validation are CardShock (42), IABP-SHOCK II (94), and ORBI (93). Recently, CS4P risk score model improved risk prediction within 24 h of CS admission beyond the IABP-SHOCK-II and CARD-SHOCK clinical risk scores (69).

6. Management

Systems of Care

CS management should start as early as possible. In the pre-hospital setting, physicians should stabilize oxygenation and circulation and treat the underlying etiology while monitoring pulse-oximetry, blood pressure, respiratory rate, and cardiac rhythm

(98, 99). All patients with CS should be rapidly transferred to a tertiary care center which has a 24/7 service of cardiac catheterization, and a dedicated ICU/CCU with availability of short-term MCS. A model, analogous to primary PCI pathways, has been proposed by the AHA, to facilitate optimal care coordination and to minimize time-delay (7) (**Figure 4**). This model consists by a network between several satellite-centers (type II and III) and a central "CS-center"(type I) (7). CS-centers should be high volume centers (>107 cases/year) (100) with highly experienced multidisciplinary team (MDT), and availability of on-site operating rooms, short and long-term MCSs, other end-organ supports and provision of safe transfer by a mobile MCS team (101-103), as these are associated with improved outcomes (100) **(Figure 4)**. A nurse to patient ratio of 1:1 is recommended (7, 104) and full integration into the post-ICU pathways.

Management of underlying cause

In CS, early identification and treatment of the underlying cause is potentially beneficial in improving outcomes. Treatment of non-ACS-causes is presented in **Table 1.**

Early revascularization strategy represents the cornerstone in the management of patients presenting with CS complicating ACS (98). In the SHOCK trial, an early invasive strategy (<12 hours post-CS onset) compared to initial stabilization conferred significantly lower all-cause mortality at 6, 12 and 60 months (105). The benefit was strongly consistent across several subgroups (age, sex, ethnicity, type of ACS, presence of diabetes) (33, 98, 106-108), leading to a current class I/B recommendation in current guidelines (98, 108).

In the CULPRIT-SHOCK trial (6), "culprit-lesion only strategy" compared to immediate multi-vessel PCI, results in a significant reduction in 30-day mortality or renal

replacement therapy (45.9% culprit-lesion-only PCI versus 55.4% immediate multivessel PCI;HR= 0.83; 95%; *p*=0.01). This was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% versus 51.5%), a consistent finding across all predefined subgroups. Thus, "culprit lesion only PCI" with possible staged revascularization has recently been implemented in the ESC-2018 revascularization guidelines (109). The lack of benefit of immediate multi-vessel PCI has been attributed to the higher doses of contrast media and prolonged procedures and is consistent at 1-year follow-up (110, 111).

Radial access when feasible (112), is currently recommended (109). The groin area often needs to be preserved for insertion of MCSs. However, the radial access may be challenging in hypotensive patients with CS, and radial access cannot be used to place temporary MCS. The implantation of DES over BMS irrespective of the clinical presentation is recommended (class I/A) (109).

Periprocedural antithrombotic management

In CS enteral antiplatelet administration may be inconsistent because of poor splanchnic perfusion and absorption, and to decreased hepatic bioactivation of thienopyridines (clopidogrel). In CS following resuscitated cardiac arrest (CA), therapeutic hypothermia induces platelet dysfunction and diminishes the bioavailability of orally administered drugs due to additional gastrointestinal dysmotility (113). Concerning the comparison of orally administered clopidogrel, prasugrel and ticagrelor, no differences were observed in terms of efficacy or safety in a secondary analysis of the IABP-SHOCK-II trial (114). However, in the absence of definitive evidence, more potent oral P2Y12 inhibitors with rapid onset of action are recommended in CS. Cangrelor IV infusion provides rapid onset of action and potential rapid reversibility because its bioavailability does not depend on hepatic and gastrointestinal perfusion.

Cangrelor has shown its safety with similar bleeding risk and efficacy with better TI-MI-flow compared with orally administered antiplatelets in a retrospective analysis of the IABP-SHOCK II trial (115). A RCT comparing cangrelor vs ticagrelor is currently running (ClinicalTrials.gov: NCT03551964). According to 2017 STEMI Guidelines (98), cangrelor may be considered in STEMI patients who are unable to absorb oral agents (IIb/A), and the same level of recommendation may be applied to patients with CS.

One small randomized trial has tested the use of glycoprotein IIb/IIIa inhibitor (GPI) abciximab in CS patients and failed to prove superiority vs standard treatment, while a prospective but non-randomized trial has showed abciximab more effective than standard treatment in patients <75 years (116, 117).

GPI use was associated with significantly higher major bleeding, regardless of randomization to cangrelor or clopidogrel, and the bleeding risk with GPI may be expected to be accentuated in patients with CS, particularly in those who require early MCS (118).

Use of IV anticoagulants is similar to patients with ACS without CS, and IV unfractionated heparin is the primary choice because of the rapid reversal and the acute renal impairment that often coexists in this setting.

Fibrinolysis

The use of fibrinolysis is according to current guidelines (98, 109), however its use may increase the risk of bleeding in the context of subsequent MCS. There is a lack of high-quality evidence to support fibrinolysis in CS. The decision to administer fibrinolysis should be individualized on the basis of perceived reperfusion benefit, bleeding risks, and the anticipated time delay to angiography. Fibrinolysis should be re-

served for STEMI patients with CS when primary PCI cannot be performed within 120 min from STEMI diagnosis (7,98).

Surgical revascularization

Although there are no direct randomized comparisons between PCI and coronary artery bypass grafting (CABG) in AMI-CS patients, a sub-analysis from the SHOCK-trial (119) suggested similar 1-year mortality between PCI and CABG (48% vs 53%) and a similar finding was found in a subsequent meta-analysis (120). The benefit of PCI is related to its early performance, but usually limited to the "culprit-lesion", while CABG achieves a complete revascularization, outweighed by the increased peri-operative morbidity. Between 2003 to 2010, the rate of early PCI in CS rose from 26% to 54%, whereas CABG rates remained relatively stable at 5% to 6% (99), which might represent current clinical practice (39).

Surgery for mechanical complications

The incidence of ventricular septum rupture (VSR) post STEMI has decreased from 1-3% in the pre-reperfusion era to 0.2% (121). Surgical closure represents the definitive treatment for post-infarction VSR, although mortality remains high (87% in SHOCK-trial) (122, 123). One study reported a sharp decrease in mortality if surgery was performed late (54.1% within 7 days from MI versus 18.4% after 7 days from MI) which is however mainly attributed to a selection bias and survival of the fittest effect (121). Survival rates following transcatheter septal closure are equally disappointing (124). While delaying of surgery is in most cases not possible because of the hemodynamic compromise secondary to the VSR, early use of MCS may allow to bridge patients to a decision of delayed repair, transplantation, or palliative options, after discussion in MDT. A substantial proportion of patients with VSR are already

hemodynamically unstable at the time of CS diagnosis and these patients have an unacceptably high mortality with an urgent/emergent surgery approach. Early use of MCS may bridge patients until a decision can be made as regard to delayed repair, transplantation, or palliative options, after discussion in MDT. Several studies suggested that early use of V-A ECMO in patients with post-infarction VSR provides hemodynamic stabilization and potential to reverse multiorgan failure (125,126). Delaying surgery, while waiting on VA-ECMO, may promote the healing process and fibrosis of the borders of the septal rupture. This could facilitate consolidation of the freshly infarcted myocardium, thus reducing the likelihood of postoperative residual shunt after surgical repair (125-128).

Papillary muscle rupture occurs in 0.25% of patients following AMI, representing up to 7% of patients with CS (129). Peri-procedural mortality associated to surgical correction of mitral regurgitation is lower than in VSR and depends on the extent of infarction and multi-organ dysfunction (99). Mitral valve replacement is preferred, as repair may be highly challenging.

Free wall rupture presents as sudden onset cardiac tamponade or cardiac arrest, with contained rupture presenting subacutely. In both cases, surgery aims pericardial drainage and closure of the ventricular wall defect (130).

Current guidelines recommend that mechanical complications should treated as early as possible after Heart Team discussion (98) (**Figure 5),** and that IABP may be considered (IIa/C) as interim support (98).

Medical Treatment

Almost one third of patients presenting with CS are “euvolemic”, but respond to fluid administration by increasing stroke volume (131). Volume responsiveness

assessment is guided by Echocardiography (**Figure 3**). Fluid administration in CS is mainly based on pathophysiological considerations and a fluid challenge with infusion of normal saline or Ringer's lactate 250ml over 15-30 min should be considered as first line treatment, if there are no signs of congestion (I/ C) (4). Careful administration of fluid boluses, and only used in conjunction with noninvasive or invasive assessment of cardiac output, is recommended in patients with CS and RV dysfunction, since excessive volume overload over-distends the RV and increase ventricular interdependence, impair LV filling and reduces systemic cardiac output (4,17).

Inotropes/ Vasopressors

More than 80-90% of patients with CS receive inotropes and/or vasopressors (5) (***Supplementary Table 2***). Vasoactive medications may restore hemodynamics, but at the cost of increasing myocardial oxygen consumption and arrhythmogenic burden. Therefore, the general recommendation on their use is to avoid when tissue perfusion is restored and limit the dose and the duration of infusion to the lowest possible (99).

In the SOAP-II trial, the predefined subgroup analysis of CS patients showed that dopamine was associated with higher 28-day mortality and increased arrhythmia burden, compared with norepinephrine (132). However, this is only hypothesis-generating since the overall trial was neutral. A recent meta-analysis suggested similar unfavorable findings when dopamine was compared to norepinephrine (133). Also in a propensity-matching-score analysis from the ESC-HF–LT-registry, dopamine was associated with worse short and long-term outcomes compared with other inotropes and vasopressors (134).

In OPTIMA-CC trial including AMI-CS patients, epinephrine was associated with a significantly higher rate of "refractory CS" compared to norepinephrine (136), and in recent meta-analysis, epinephrine use for hemodynamic management of CS was associated with a threefold increase of risk of death (137). Additionally, epinephrine during resuscitation for CA failed to improve survival with good neurologic outcome when compared to placebo (138). All these data suggest norepinephrine should be the first-line vasopressor recommended by guidelines (IIb/B) to sustain perfusion pressure (4), while we do not recommend routine use of dopamine or epinephrine in CS. "Vasopressin is a non-sympathomimetic vasoconstrictor agent that increases systemic vascular resistance (SVR) and mean arterial pressure (MAP) but doesn't did not affect pulmonary vascular resistance. Vasopressin increases systemic arterial pressure by specifically inhibiting the same intracellular enzymes responsible of vasodilator action of milrinone and may be used to counteract vasodilation caused by milrinone (138). In combination with Milrinone, administration of vasopressin at low doses increased the systolic pressure and allowed discontinuation or a decrease in catecholamine vasopressors (139).

The addition of an inotrope (dobutamine) is recommended with a class IIb/C recommendation, reflecting the paucity of data in this setting (4).

Levosimendan (140) may be used in particular CS patients already on chronic beta-blocker therapy (17, 99), as well as in patients with CS and acute RV failure or pulmonary hypertension (PHT), owing to its favorable effects on pulmonary vascular resistance (141, 142). The inotropic effect of levosimendan is the result of a combined effect from both calcium-sensitization and selective and potent PDE3 inhibition. (143-146).

Milrinone had similar effectiveness and safety profiles compared to dobutamine (147), but safety concerns over its use in ischemic aetiology warrant caution owing to the results of the OPTIME-CHF trial in decompensated HF patients (148).

Mechanical Circulatory Support (MCS)

Temporary MCS) (**Table 2)** has an emerging role in CS. Current guidelines (4) recommend the early use of MCS in patients with CS refractory to fluid load and inotropes/vasopressors (IIb/ C), as bridge either to recovery, re-evaluation, transplantation or a permanent implanted left ventricular assist device (LVAD) (149). However, MCSs are associated with significant complications (**Table 2**), require specialist multidisciplinary expertise for implantation and management, and high-quality evidence regarding outcomes is largely absent.

IABP produces a modest increase in CO of 0.5-1 L/min and may have even less benefit in patients with tachycardia and irregular rhythms. RCTs were performed only in AMI-CS patients and in the IABP-SHOCK-II trial (3) IABP failed to demonstrate benefit on mortality or any of the secondary endpoints. A meta-analysis including 12 RCTs and 15 registries, showed no survival benefit after IABP in AMI-CS, and has further called into question the utility of IABP therapy (150). Recently, the 6-year follow-up of IABP-SHOCK-II didn't show any benefit on long-term survival (151). Therefore, 2017-ESC-STEMI guidelines gave III/B recommendation for the routine use of the IABP in CS but still consider IABP only in patients with mechanical complications (IIa/C) or to stabilize for transfer for higher-levels of MCS (98). IABP still remains the most commonly used MCS, and in the light of new data showing more vascular and bleeding complication and possible higher mortality with other devices, the class III indication of IABP probably need to be reconsidered.

Impella is a microaxial pump giving only left-sided support, that unloads the LV by expelling blood flow from the LV into aorta and may provide up to >5L/min of blood-flow depending on the device used and depending on afterload (149, 152, 153). Impella 2.5 and Impella CP can rapidly be implanted percutaneously in the catheterization laboratory while Impella 5.0 requires surgical cannulation (154). Unlike IABP, Impella does not require EKG or arterial waveform triggering, facilitating stability even in the setting of tachyarrhythmias or electromechanical dissociation. Although providing superior hemodynamic support compared to IABP, there is no evidence of survival benefit in AMI-CS, largely due to vascular and bleeding complications (155). In addition, a propensity-matched study showed no survival benefit with Impella use and significantly more complications (156). More recent large-scale registries using propensity-matching, showed even higher mortality with Impella use which was also accompanied by more bleeding and access site complications (157, 158). Therefore, the broad use of the Impella in unselected cases should be avoided and larger RCTs addressing survival benefit, timing of implementation (pre/post- revascularisation) and mechanism of benefit are needed. The DanGer Shock study (159) will be the first adequately powered RCT to address whether Impella-CP will improve survival in AMI-CS.

High quality evidence regarding Impella in other causes of CS is also lacking, however in the RECOVER-I study, including patients with CS-postcardiotomy, the Impella 5.0 was associated with 94%, 81%, and 75% survival at 30-days, 6-months, and 1-year, respectively (160).

The Tandem-Heart provides a continuous flow (4L/min) via a centrifugal pump. The venous cannula is inserted through the femoral vein and is advanced via transseptal puncture into the left atrium (LA), and arterial cannula provides oxygenat-

ed flow into the abdominal aorta or iliac arteries. In two randomized studies, including AMI-CS patients, Tandem-Heart significantly improved hemodynamic indexes as compared to IABP, but 30-day mortality did not differ between the two groups (161, 162).

VA-ECMO provides cardiopulmonary support by draining venous blood from the right atrium and returning it after oxygenation to the ascending aorta (central cannulation) or to the iliac artery (peripheral cannulation). “VA-ECMO provides high levels of biventricular cardiac (V-A) and respiratory support (V-V) in a large spectrum of clinical settings, including CS patients with malignant arrhythmia and CA.” Some studies indicated an improvement in microcirculation as measured by side-stream dark field imaging (163, 164). The improvement in the oxygenator membranes permitted low resistance and improved blood compatibility characteristics (17, 165). The modern centrifugal pumps generate less heat and are less thrombogenic, allowing extended duration of support (165).

In the event of very poor LV function, peripheral VA-ECMO can be associated with progressive LV distension and pulmonary congestion, potentially resulting in impaired myocardial recovery (165, 166). Decompression strategies for LV venting include additional procedures, such as, IABP, Impella, septostomy and hybrid circuit configuration (165, 166, 168).

When cardiac recovery precedes pulmonary recovery, ejection of deoxygenated blood flow into the ascending aorta results in upper body hypoxia - “Harlequin syndrome” (169), requiring reducing cardiac ejection or reconfiguration (VVA or VAV) until the lungs recover.

In two recent meta-analysis including CS and CA patients, VA-ECMO was associated with significantly improved 30-day survival in both groups compared with IABP, but no difference when compared with Tandem-Heart or Impella (170), A large registry with a 9-year observational period suggests 30-day in-hospital mortality remained unchanged over time (59.0% in 2007–2012 versus 61.4% in 2013–2015) (171).

Ongoing randomized clinical trials in post MI-CS, will test whether VA-ECMO on top of revascularization and standard therapy will lead to a reduction in mortality (172).

Isolated RV support

Right-sided support with either Impella-RP or Tandem-Heart RA-PA has been described in numerous case reports. RV support with Impella-RP in patients with refractory RV failure, was feasible and associated with early hemodynamic benefit, in a small non-randomized study, RECOVER-RIGHT (173). Future RCTs will test whether RV support for either RV pressure unloading (Impella RP 4L/min) or RV volume unloading (TandemHeart RA-PA) will improve clinical endpoints (154). However, the clinical benefit of Impella-RP in real-world clinical practice is largely unknown. Recently in a Letter to Health Care Providers, US-FDA provided an update about Impella data based on the results of post approval studies, where the interim analysis has indicated that survival at 30 days post device explant or discharge, was 33.3 %. (174).

“The recently introduced Protek Duo dual-lumen cannula contains 2 lumens, one serving as an inflow cannula and is positioned via internal jugular vein into the RA, the second delivering blood into the main PA. Blood is drained from the RA into an extracorporeal centrifugal pump, which delivers blood back to the PA. There are no

large observational studies or randomized data, but several case reports described use of the device for CS secondary to RV failure in the setting of LVAD implantation and CS resulting from decompensated severe pulmonary hypertension (175-177).

Temporary MCSs represent a therapeutic modality that is available as a bridge to recovery or as a bridge to decision in refractory cases (178). However, despite of initial beneficial effect on BP and arterial lactate (179), the unselected use of active MCS in patients with CS is not supported since data on patients' selection are still scarce, the results of most trials or meta-analyses were at best neutral on survival and the costs (in terms of patient morbidity/mortality, as well as healthcare economics) are high and unproven. Although, risk scores such as SAVE and ENCOURAGE have been used to predict survival after the insertion of VA-ECMO (95)(96), MCS are associated with severe complications that may counterbalance beneficial hemodynamic effects, and further research is needed to establish a better risk/benefit ratio. This is of utmost importance in particular groups of patients such as elderly, patients with long duration of CS, or patients with multiple comorbidities. The neutral results of the existing RCTs have multiple explanations related to inclusion of heterogeneous population, large variability in timing of intervention, different learning curves of institutions, lack of data regarding level of anticoagulation, and poorly defined endpoints. The observed improvement of macrocirculation will not automatically translate to improved microcirculation, and macrocirculatory improvements should be considered as a measure of technical success rather than an endpoint. Clinic relevant endpoints, such as 30-day and 180-day mortality should be considered in future RCTs. A "standardized team-based approach" using predefined algorithms for early MCS implant, should be also investigated in clinical trials. In a recent study, implementation of a "multidisciplinary team-based approach" including mandatory invasive hemodynam-

ics and appropriate use of MCS, resulted in improved survival in patients with CS. Compared with 30-day survival of 47% in 2016, before implementation of this strategy, 30-day survival rate in 2017 and 2018 increased to 57.9% and 76.6%, respectively (180).

In addition, future studies should address the choice of an individual type of MCS as well as the markers of monitoring during MCS (hemodynamic markers, echocardiography markers, inflammatory response or organ damage markers) that can guide weaning and final decisions (181).

Currently, the monitoring is primarily based on Echocardiography, PAC hemodynamics, lactate and organ function tests. In clinical practice, if the patient is stable, weaning starts from vasopressors followed by a reduction of levels of support. If the patient remains stable on low-level of support and without requiring higher doses of vasopressors/inotropes, the MCS can be explanted (178). In case of MCS complications, vasopressor is continued to allow removal of the device. When the patient is hemodynamically unstable on initial MCS, a combined support may be considered. Especially in patients with biventricular failure and severe hypo-oxygenation, combined VA-ECMO and Impella may be considered. Duration of support is often unpredictable, and weaning should incorporate evaluation of bridging strategies. Patients who cannot recover on temporary MCSs, but without irreversible end-organ damage should be directed to a permanent modality (durable LVAD or heart transplantation) (131).

Organ Dysfunction and specific non-cardiac interventions

Mechanical Ventilatory Support

Acute respiratory failure is present in almost all patients presenting with CS. Hypoxemia and hypercapnia are the consequence of intrapulmonary shunting generated by pulmonary congestion, the reduction in lung space with increasing the ventilation–perfusion mismatch, and alteration of respiratory drive as result of cerebral hypoperfusion. In addition, lactic acidosis increases the compensatory respiratory load with hyperventilation, thereby augmenting total body oxygen requirements (182).

Hypoxemia is addressed with conventional oxygen therapy in various inflow rates, with one third of the patients (usually with less severe hemodynamic impairment) successfully managed via this approach (183). 60 to 80% of the patients develop progression of respiratory failure requiring invasive MVS (1) and these patients have worse prognosis (184). Decision to initiate MVS is multifactorial, including arterial blood gas levels, neurologic status and required interventions.

No specific ventilation modality has demonstrated superiority over the others (185). However, high levels of PEEP are poorly tolerated, particularly in patients with RV dysfunction. If invasive ventilation is required, lung-protective ventilation (6 mL/kg/ body weight tidal volume) should be undertaken to prevent pulmonary injury (17, 182, 186).

In CS associated with RV dysfunction, permissive hypercarbia/hypoxaemia should be avoided due to the associated pulmonary vasoconstriction. Also, positive intrathoracic pressure should be generally avoided because it worsens RV failure. However, the final decision will depend on the clinical needs to weigh the risks and benefits of the impact of ventilation on hemodynamics, severity of hypoxemia and presence of atelectasis (186).

Liver injury

Liver injury frequently complicates CS, and >50% of patients present with elevated liver enzymes (187). Ischemic hepatitis represents the diffuse hepatic injury caused by a sudden drop in CO and is accompanied by a sharp elevation of the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH). Aminotransferases peak ≈1 to 3 days after the hemodynamic insult returning to normal 7-10 days in the absence of further insult. Transaminases are associated with worse in-hospital mortality and can be used as biomarkers of hemodynamic reserve (188). Congestive hepatopathy is commonly seen in patients with high venous pressure, particularly in CS patients with RV dysfunction. It is accompanied by high levels of direct bilirubin, gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). However, these abnormalities often coexist, and liver function abnormalities in CS are a combination of both congestion and reduced cardiac output. In the absence of specific therapies for liver injury in CS, particular attention must be paid to RV function, including reduction in pulmonary vascular resistance and right atrial pressure (186, 187).

Renal Dysfunction

About one third of CS patients develop acute kidney injury (AKI), but many CS survivors do experience gradual renal recovery. The process may be slow (5-20 days) and depends on severity of AKI (189). Systemic hypoperfusion, backward congestion, nephrotoxic drugs, contrast agents and MCS may contribute to AKI in CS. If acute tubular necrosis develops renal replacement therapy (RRT) will be required and prognosis worsens.

Continuous veno-venous hemodiafiltration (CVVHDF) is recommended in severe AKI (creatinine ≥2× baseline and urine output <0.5 mL/kg/h for ≥12 hours) or when life-threatening changes in fluid, electrolyte, and acid-base balance mandate (190). Intermittent hemodialysis should not be used as it is poorly tolerated (191).

Temperature Management

An admission diagnosis of cardiac arrest (CA) increased progressively the risk of hospital mortality among patients with each SCAI shock stage, supporting its inclusion as an effect modifier in the SCAI shock classification schema. However, the relative effect of CA on mortality appeared to be greater among patients with mild CS or "at risk" of CS (SCAI stages A through C), categories where therapeutic interventions may have more benefit (19).

Following CA, targeted temperature management reduces the overall metabolic rate and myocardial oxygen consumption contributing to better neurological protection (192,193). However, the data is limited in CS following CA. In the SHOCK-COOL trial, mild therapeutic hypothermia failed to show a substantial beneficial effect on cardiac power index at 24 hours in patients with CS after AMI (194). The HYPO-ECMO trial (195) is currently recruiting CS patients on VA-ECMO and will address whether moderate hypothermia is associated with improved organ function.

VI. Stabilization phase - Discharge

Patients discharged at home without having fully recovered from critical illness carry a very high rate of early re-hospitalization and death (196, 197). A MDT approach before discharge is mandatory, in order to address psychosocial aspects, educate in

terms of symptoms, diet, exercise, manage comorbidities (198) **(***Supplementary Table 3***).** In patients with HF and reduced ejection fraction, disease-modifying therapies should be re/initiated at lowest doses when patients are clinically stable, euvolemic and at least 24 hours after IV catecholamines stopped. When the patient cannot be discharged home, a rehabilitation program or a palliative care center should support the transition phase (7).

CS in various clinical settings

In patients presenting with CS, non-ACS causes, should always be considered, as they represent different clinical settings with particular pathophysiological characteristics and specific management (**Table 1**).

RV failure

Rapid identification of the presence and aetiology of RV dysfunction, correction of hypervolemia/hypopvolemia, appropriate management of ventilation and assessment of associated PHT are pivotal to successful management. (**Table 1**). Echocardiography and PAC-tailored management are recommended to optimize hemodynamics and volume status. When patients fail to respond to inotropes/vasopressors, VA-ECMO or Impella-RP may be considered (172). Acute RV failure post LVAD implantation has an incidence of 20-25% and may be clinically recognized and diagnosed using the modified EUROMACS score (including clinical, laboratory, echocardiographic and hemodynamic variables) (199). It should be managed with standard supportive therapies including inotropes like milrinone, levosimendan and dobutamine, which allow pulmonary vasodilation (200). Inhaled NO and sildenafil can be used to reduce PVR. The LVAD flow must be adjusted in order to optimize RV func-

tion. In severe cases, right-sided mechanical support should be used (Impella-RP or Protek-duo). The ideal device for RV support should be one that is easy to implant and explant, provides adequate RV support and doesn't interfere with LVAD physiology (177). VA-ECMO should be used with caution because it concurrently decreases LVAD preload and increases LVAD afterload. (**Table 1**).

Fulminant myocarditis

The combination of flu-like symptoms in association with evidence of myocardial injury should raise the suspicion of acute myocarditis. The diagnostic approach In the critically ill patient with rapidly progressive HF despite standard therapy includes RV endomyocardial biopsy to exclude giant cell myocarditis (GCM) and acute eosinophilic myocarditis (AEM), where treatment with immunosuppressant agents (201, 202) should not be delayed. In a prospective study, combination therapy (cyclosporine plus prednisolone) was associated with more favorable outcome (201). The contemporary transplant-free survival of otherwise lethal giant-cell myocarditis treated with combined immunosuppressive drugs is 65% at one year and 42% at five years (202). In contrast to GCM, AEM usually responds to high doses of corticosteroids (203).

In patients with fulminant myocarditis, irrespective of the underlying aetiology, early MCS should be considered, and is associated with acceptable mid-term survival rates (203,204). Due to the diffuse myocardial involvement, percutaneous univentricular MCS are often insufficient to restore peripheral perfusion and oxygenation, and biventricular support (VA-ECMO in combination with Impella, or a BiVAD) is frequently required (203). Where myocardial function does not sufficiently recover, longer-term MCS may be required, potentially followed by transplantation.

Takotsubo Syndrome

Takotsubo syndrome is characterized by severe AHF often accompanied by LV outflow-tract obstruction (LVOTO), CS and cardiac arrest (CA). The incidence of CS in the Takotsubo population varies from 2.8 to 12.4% (205, 206). In a large-scale study comparing clinical characteristics and in-hospital outcomes of patients with CS in settings of Takotsubo Syndrome vs patients with AMI-CS, CS in Takotsubo was associated with a significantly lower mortality (15%) than AMI-CS (36.5%) (40). In a prospective study with longitudinal follow-up, patients with Takotsubo and CS had a 28-day and 1-year mortality of 28.6% and 61.9%, respectively (206). Long term susceptibility to fatal events after the acute phase of Takotsubo Syndrome may be explained by a LV function not yet fully recovered and/or arrhythmic events caused by QT-interval prolongation (206). Regarding the treatment, catecholamine administration should be avoided, as already have a causative relationship with the syndrome. Milrinone, via increasing cardiomyocyte cAMP levels, also appears to trigger Takotsubo in preclinical models and should be avoided (207). Levosimendan, which do not increase cAMP seems a rational approach (208). Early MCS may diminish the need for catecholamines and provide the reasonable time frame for LV recovery (178). Afterload reduction by IABP may further deteriorate the LVOT obstruction and close echocardiographic monitoring is required.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurring in the last month of pregnancy or in the puerperium, with unpredictable outcome. In the majority of cases myocardial function recovers within months, while in about one third of it stabilizes or worsens (209). Some PPCM patients may have thrombus in the LV that may lead to stroke. The pathophysiologic trigger is the formation of 16 kD prolactine that promotes oxidative stress. In CS complicating PPCM, catecholamine ther-

apy is detrimental. Although, the evidence is provided only by small studies, the combination of high dose bromocryptine (inhibitor of prolactin production), inodilators and early MCS seems to be a rational strategy (210).

Valvular Disease

A variety of mechanisms may contribute to CS in the setting of decompensated valvular disease and initial stabilization is recommended before evaluation for corrective surgery. For patients with aortic or mitral valve endocarditis with severe acute regurgitation, obstruction or fistula causing refractory CS, surgery must be performed on an emergency basis, irrespective of the status of infection (211). MCS should be individualized based on pathophysiology of the valvular disease (172) (**Table 1**).

Out of hospital cardiac arrest (OHCA)

OHCA patients represent a special category, with increasing prevalence in the ICCUs. The prevalence of CA increased substantially with increasing shock stage in SCAI classification, highlighting the correlation between CA and severe shock. Shock severity demonstrated a stepwise association with mortality in patients with CA, emphasizing the synergistic mortality effects of concomitant CS and CA (19).

In the IABP-SHOCK-II and the CULPRIT-SHOCK trials 40-50% of patients were resuscitated before randomization (3, 6). Immediate mortality is high, reaching more than 85% in some registries (212). During hospitalization, many of these patients also die from withdrawal of life sustaining therapies because of anoxic brain injury.

Pathophysiology of CS secondary to CA is determined by pump failure (as result of the initial cardiac insult responsible by CS and prolonged myocardial stunning due to CA) and systemic vasodilation secondary to regional and global ischemia-reperfusion

injury (213, 214). For patients with CA refractory to CPR, E-CPR (ECMO support during CPR) may be considered. The goal of E-CPR is to support patients in refractory CA while reversible causes are being identified and treated (215-217). Based on registry studies (171), E-CPR was associated with a 13% absolute increase in the 30-day survival rate compared to conventional CPR.

These patients have a higher burden of in-hospital complications with more frequent use of resources (218) and 30% are discharged with functional impairment, requiring a skilled nursing facility (219).

Post-cardiotomy cardiogenic shock (PCCS)

The incidence of PCCS varies between 2% and 5% (220-222) and it is associated to poor outcomes. In a study including 1764 PCCS patients, 30-day and 3-months survival were 61 and 35%, respectively, with only 29% alive at 1 year (223). Numerous factors may contribute to PCCS, including pre-operative morbidity, type of surgery, insufficient cardio-protection and prolonged cardiopulmonary bypass. Inability to wean from cardiopulmonary bypass and/or poor postoperative hemodynamics may be indications for MCS. Depending on the pathophysiology, VA-ECMO, Impella 5.0 or Centrimag can be used in PCCS (153,154).

Refractory RV failure occurs in 0.1-1% of patients following cardiotomy and in-hospital survival is as high as 25-30% (224).

Two readily remediable conditions must be rapidly excluded/addressed including localized pericardial tamponade and dynamic left-ventricular outflow tract obstruction. The localized tamponade in the first week post cardiotomy has been reported at 0.2-2% of patients with CABG and 8.4% in heart transplant patients, and precipitating

factors included administration of anticoagulants, coagulation disorders, excessive mediastinal bleeding, the removal of epicardial pacing wires (225).

Dynamic LVOTO leading to CS in the first days post-surgery has an incidence of 0.3% and associated conditions are hypovolemia, cardiac hypertrophy, aortic valve replacement, and high doses of catecholamines (225).

Cancer

Although data regarding the incidence of CS in patients with a malignancy are scarce, history of cancer is an independent risk factor of mortality in CS (226). CS can develop due to cancer itself, the co-existing cardiovascular disease, thromboembolic events, or the type of treatment (surgery, chemotherapy, immune checkpoint inhibitors and radiotherapy) (227).

Gaps in Evidence

Despite advances in revascularization, valve interventions and MCSs, CS remains the most common cause of in hospital death after AMI and a major cause of death in young patients with other potentially reversible underlying cardiac pathology. Gaps in evidence are extensive **(Table 3**) and relate to the definition, phenotype diversity, pathophysiology and management. These gaps contributed to a large geographical variability in practice care, in terms of utilization of decisional markers or risk-scores, use of hemodynamic monitoring, and timely deployment of MCS. Recently, the National Cardiogenic Shock Initiative (NCSI) designed a shock protocol and organized teams who mutually agreed to treat patients according to the "best practices"(74). This initiative suggests that a protocol-based approach is reproducible and

that overall adherence to the protocol may be associated with improved outcomes (74). A standardized "team-based" multidisciplinary care in the context of a network of regionalized care system may not only improve patient outcomes but may also facilitate pragmatic trial designs evaluating current and future novel therapies (180).

Evidence from RCTs is limited, mostly because small numbers of patient are recruited, with only approximately 2000 patients being randomized in CS trials. In addition, blinding is often not possible and the primary endpoints often differs from one study to another. Designing outcome trials in CS remains particularly challenging in this critical, rare and very costly scenario in cardiology.

Summary

CS is a complex multifactorial clinical syndrome with extremely high mortality, developing as a continuum, resulting from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. Substantial investments in research and development have not yielded proof of efficacy and safety for most of the therapies tested, and outcome in this condition remains poor. Future studies should consider delivering pathophysiological appropriate therapies in a timely manner, in appropriately selected population, whilst avoiding iatrogenic harm. High quality translational research should facilitate incorporation of more targeted interventions in clinical research protocols, aimed to improve individual patient outcomes.

Conflict of interest

O.C. reports grants from Servier, grants from Novartis, grants from Vifor, other from Boehringer, outside the submitted work; **J.P.** received horonaria from Orion Pharma, Roche Diagnostics, Novartis, Pfizer and Servier, outside of submitted work; **A.M.** reports personal fees from Orion, grants and personal fees from Roche, personal fees from Servier, personal fees from Otsuka, personal fees from Philips, grants and personal fees from Adrenomed, personal fees from Neuro Tronik, grants and personal fees from 4TEEN4, personal fees from Sanofi, outside the submitted work; **J.B.** reports personal fees from Novartis, personal fees from BMS, personal fees from Pfizer, grants and personal fees from Vifor, grants and personal fees from Bayer, personal fees from Servier, personal fees from Orion, grants and personal fees from CvRX, personal fees from MSD, personal fees from Boehringer Ingelheim, personal fees from Astra Zeneca, grants and personal fees from Abiomed, personal fees from Abbott, grants and personal fees from Medtronic, outside the submitted work; **VP.H** reports personal fees from Orion Pharma, outside the submitted work; **JC** reports personal fees from Roche, personal fees from Servier, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Berlin-Chemie, outside the submitted work; **S.P.C** reports personal fees from Boehringer Ingelheim, personal fees from Vixiar, grants from Astra Zeneca, grants and personal fees from Bristol-Myers Squibb, outside the submitted work; **L.L** reports personal fees from Merck, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, grants and personal fees from Novartis, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, personal fees from Medscape, personal fees from Myokardia, grants and personal fees from Boehringer Ingelheim, outside the submitted work; **A.R.L** reports grants and personal fees from Servier, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from Roche, personal fees from Takeda, personal fees from Boehringer Ingelheim, personal fees from Amgen, personal fees from Clinigen Group, personal fees from Ferring Pharmaceuticals, personal fees from Eli Lily, personal fees from Bristol Myers Squibb, personal fees from Eisai Ltd, outside the submitted work; **M.M** reports personal fees from Honoraria for speeches from Abbott and Edwards, from Honoraria as trials' committe or advisory board member from Abbott, Actelion, Amgen, bayer, Fresenius, Novartis, Servier, Vifor for minimal amounts in the last 3 years, outside the submitted work; **M.P** reports personal fees and non-financial support from Novartis, personal fees from Servier, non-financial support from Vifor, outside the submitted work; **S.D.A** reports receiving fees from Abbott Vascular, Bayer, Boehringer Ingelheim, Cardiac Dimension, Impulse Dynamics, Novartis, Servier, and Vifor Pharma, and grant support from Abbott Vascular and Vifor Pharma, outside of sub,itted work; **G.F** reports other from Committee Member in trials sponsored by Medtronic, Vifor, Servier, Novartis, BI, outside the submitted work; **F.R** before 2018 reports grants and personal fees from SJM/Abbott, grants and personal fees from Servier, personal fees from Zoll, AstraZeneca, Sanofi, grants and personal fees from Novartis, personal fees from Amgen, BMS, Pfizer, Fresenius, Vifor, Roche, Cardiorentis, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, other from Heartware, grants from Mars, outside the submitted work; since the 1st January 2018 no personal payments and al payments directly to the University of Zurich; **A.J.S.C** reports personal fees from Astra Zeneca, personal fees from Bayer, personal fees from Menarini, personal fees from Novartis, personal fees from Nutricia, personal fees from Servier, personal

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Figure Legend:

Figure 1. Classifications of CS.

A. The first two classifications are based on clinical severity and the response to the treatment and are presented with possible overlapping.

B. When patients are classified by hemodynamic phenotypes, low CI is a common finding, but ventricular preload, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and systemic vascular resistance (SVR) may vary.

CS caused by predominant left ventricular (LV) failure may present as "cold-wet" (hypoperfused and congested) with high SVR and PCWP (2/3 of clinical presentations in SHOCK trial. Patients decongested may present as "cold-dry" (hypoperfused without congestion) with high SVR and relatively normal LV and right ventricular (RV) filling pressures. Up to 20% of CS patients may present as "wet and warm", with high PCWP but low SVR. These patients may have excessive vasodilation as a result of systemic inflammatory response syndrome (SIRS) or mixed shock and most of them had fever and leukocytosis, but not all had proven infection.

CS caused by predominantly RV failure may present as "wet-cold" or "wet-warm". These patients have high RV filling pressure, increased CVP/PCWP ratio, and different values of SVRs according to the extent of systemic inflammatory response. Pulmonary artery pressure (PAP) is usually low or normal in patients with predominant pump failure as the origin of right ventricular CS such as in RV acute myocardial in-

farction, RV cardiomyopathies and tricuspid valve rupture. On the other hand, an elevated PAP will be encountered in patients with pulmonary embolism, primary and secondary pulmonary hypertension.

Abbreviations: *CP=cardiac power; CPR= cardio-pulmonary resuscitation CS=cardiogenic shock; CVP=central venous pressure; ECMO= extracorporeal membrane oxygenation; IABP=intra aortic balloon pump;MCS=mechanical circulatory support; MODS=multi-organ dysfunction syndrome; PA=pulmonary artery; PCWP=pulmonary capillary wedge pressure; SBP=systolic blood pressure; SVR=systemic vascular resistances.*

Figure 2. Pathophysiology of CS with staged abnormalities of clinic examination, hemodynamics, microcirculatory dysfunction and organ failure. On upper row is presented SCAI classification.

Abbreviations: *Ac=arteriolar constriction; Ad= arteriolar dilatation; ACM= alveolar-capillary membrane; ALT=alanine aminotransferase; AST=aspartat aminotransferase; BUN=blood urea nitrogen; CI= cardiac index; DIC=disseminate intra-vascular coagulation; eGFR= estimated glomerular filtration rate; GGT= gmma glutamyltransferase; SBP=systolic blood pressure;; SVR=systemic vascular resistance; Vc=venous constriction; Vd= venous dilation; SIRS= systemic inflammatory response syndrome; TMAO=trimethylamine N-oxide;*

Figure 3. Utility of echocardiography in the diagnosis and management of patients with cardiogenic shock

Abbreviations: *AMI=acute myocardial infarction; AV=aortic valve; CABG=coronary artery bypass graft; CI=cardiac index; ED=emergency department; EF=ejection fraction; ICCU= intensive cardiac care unit; ICU intensive care unit; IVC=inferior vena cava; LV=left ventricle; LVOT=left ventricular outflow tract; LVOTO= left ventricular outflow tract obstruction; MCS= mechanical circulatory sup-*

port; SAM=systolic anterior motion of mitral valve; MR=mitral regurgitation; PFO=persistent foramen ovale; PCI=percutaneous coronary interventions; PH=pulmonary hypertension; PUS=pulmonary ultrasounds; RV=right ventricle; VTI-LVOT= velocity time integral- left ventricular outflow tract; TR=tricuspid regurgitation.

Figure 4. The Systems of Care for CS patients.

A model for minimizing time delays and optimizing care has recently been proposed by the American Heart Association, where a network between several satellite-centers and a central "CS-center" exists to facilitate optimal care coordination. The core-center (first level) should be a dedicated CS center, with expertise in the use of invasive hemodynamics and advanced MCS and should be linked with multiple satellite centers (3rd level triage hospitals or 2nd level PCI capable centers).

Patients should be transported to the nearest hospital capable of performing 24/7 PCI and ICU/CCU availability in order to stabilize haemodynamics (type II center). "Refractory" CS patients needing MCSs will be directed to a higher level of care (type I-CS center). The patient should be hospitalized in ICU/CCU depending on hospital availability, and followed by physicians experienced in cardiovascular procedures. CS centers should also be able to provide safe transfer by a mobile extracorporeal membrane oxygenation (ECMO) team (out-of-hospital to hospital or inter-center transfer), which is a feasible and effective strategy in selected patients. Patients that recover and stabilize should be discharged home or directed to rehabilitation or palliative care centers, depending on the needs.

Figure 5. The algorithm for pre- and in-hospital management of patients with CS.

The level of decision by multidisciplinary heart team is presented in red rectangles.

Abbreviations: *AMI=acute myocardial infarction; BGA=blood gas analysis; CA=cardiac arrest; CABG=coronary artery bypass grafting; Dob=dobutamine; GDMT=guideline-directed medication therapy; HfrEF=heart failure with reduced ejection fraction; IABP=intra-aortic balloon pump; IMV=invasive mechanical ventilation; LVAD=left ventricular assist devices ;MCS=mechanical circulatory support; MR=mitral regurgitation; MV=mitral valve; NE=noradrenaline; NV=native valve; PAC=pulmonary artery catheter; PCI=percutaneous angioplasty; PV=prosthetic valve; PCS=postcardiac surgery; RRT=renal replacement therapy; RV=right ventricle; VSD=ventricular septal defect; TTM=temperature management; ;*

A.Clinical classifications of CS

preCS

Hypoperfusion and SBP> 90 mmHg without circulatory support

CS

Hypoperfusion and SBP <90 for >30 min or the need for pharmacologic or IABP to maintain SBP >90 mm Hg or MAP with 30 mm Hg lower than baseline.

Refractory CS

Ongoing evidence of tissue hypoperfusion despite administration of adequate doses of 2 vasoactive medications and treatment of the underlying etiology

A-At risk

At risk of CS;
SBP=N;CI>2.5;
Lactate=N
No hypoperfusion

B-Beginning

Relative hypotension or tachycardia without hypoperfusion;
CI<2.2,PA sat ≥65%.
Lactate<2mmol/l

C-Classic

Hypoperfusion that requires an initial set of Interventions (inotropes, pressor, MCS, or ECMO) beyond volume resuscitation to restore perfusion; CI<2.2,PA sat <65%,CP ≤0.6. Lactate>2mmol/l

D-Deteriorating

Failed to stabilize despite intense initial efforts. After >30 minutes the patient has not responded with resolution of hypotension or end-organ hypoperfusion. Further escalation (increase in the number and intensity of IV therapies, or addition of MCS) is required;
Lactate>5mmol/l

E-Extremis

refractory cardiac arrest with ongoing CPR or are being supported by multiple acute interventions including ECMO-facilitated CPR

Lactate<2mmol/L → ← Lactate>2mmol/L →

Hypoperfusion

MODS

B. Hemodynamic classification of CS

SVR ↓;PCWP N ↓;CVP N ↓ **“warm-dry”**	SVR ↓;PCWP ↑;CVP ↑ **“warm-wet”**
SVR ↑;PCWP N ↓;CVP N ↓ **“cold-dry”**	SVR ↑;PCWP ↑;CVP ↑ **“cold-wet”**

Initial cardiac insult

Stage A | Stage B | Stage C,D,E

clinic

Congestion

hemodynamic

Hypoperfusion

vasoconstriction → | ***vasodilation*** →

SBP=N
CI=N

SBP↓
SVR=N/↑

SBP=N/↓
SVR↑↑

SBP↓
SVR=N/↓

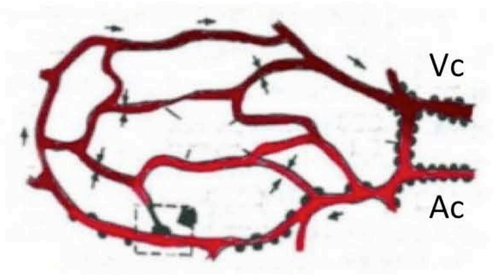
SBP↓↓
SVR=↓

SBP↓↓
SVR=↓↓

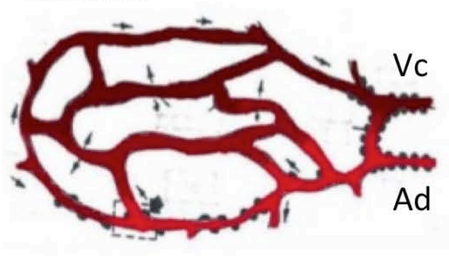
SBP↓↓
SVR=↓↓↓

microcirculation

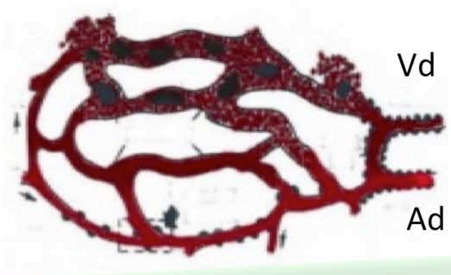
Constriction of arterioles
Constriction of venules
Closed true capillaries
Maintain drive pressure



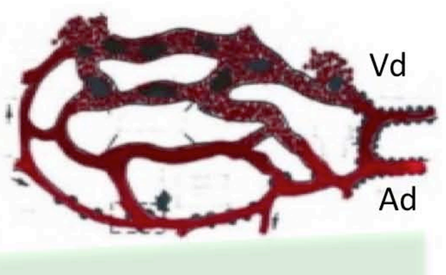
Dilatation of arterioles
Constriction of venules
Opening of true capillaries
Microcirculatory stasis
Acidosis



Paralytic dilatation
Capillary stasis
Microthrombosis
↑permeability
↑↑Acidosis



Paralytic dilatation
Microthrombosis
↑permeability
↑↑Acidosis
Mitochondrial loss

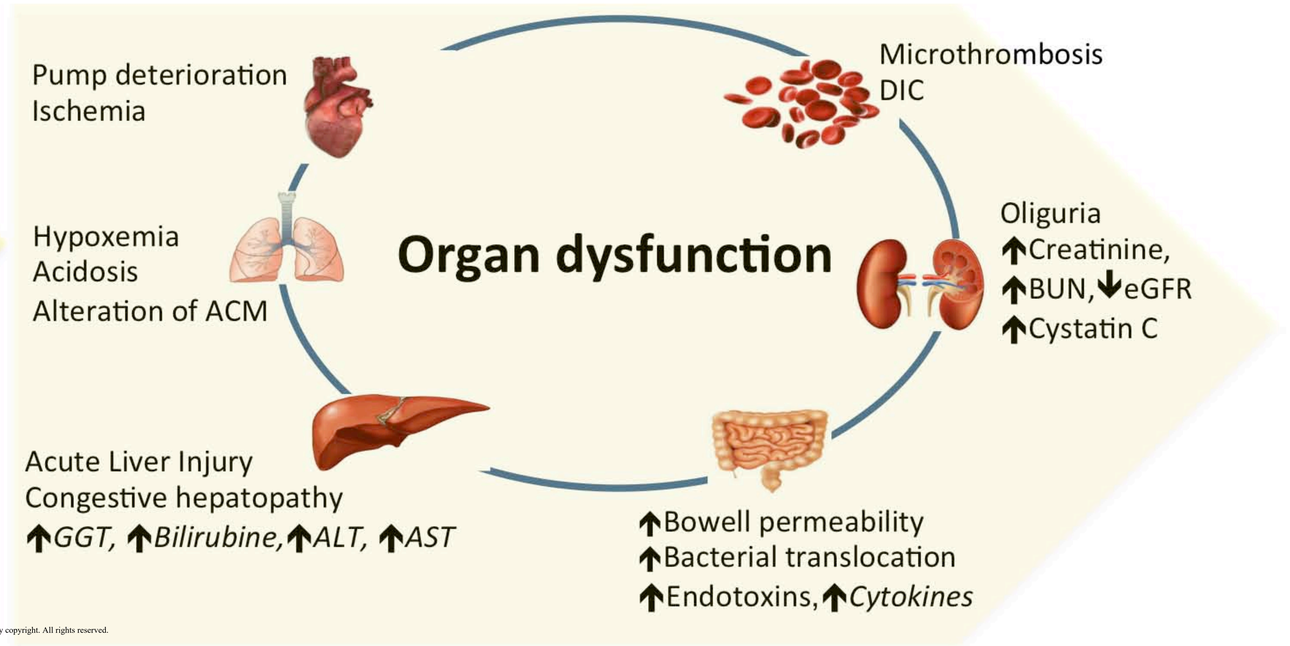


SIRS

Inflammation

Organ dysfunction

Organ injury



First line echo diagnosis (prehospital, ED) FoCUS protocols

Identify type of SHOCK:
obstructive – pericardium
distributive-sepsis
cardiogenic - search for etiology, define anatomy
(severe LV and/or RV dysfunction
severe valve dysfunction
AMI mechanical complications)

Estimate LV/RV filling pressure:
Left -B-lines(LUS)
Right-IVC diameter, Collapsibility Index

Second line echo diagnosis (ICCU, CICU):comprehensive Echo*

Etiology
-Confirm diagnosis
-Indication and timing for corrective interventions (PCI, CABG, valve surgery)

Describe Hemodynamics
Cardiac output decrease,
RV and LV contractility;
LV and RV filling pressures
Pulmonary pressure

Guide choice of therapies and assess response to interventions
(fluids, inotropes, pacemaker optimization, MCS)
-LV and RV diastolic diameters
-LV filling pressure(e/e',B-lines), RV filling pressures (IVC diameter, CI)
-LV and RV contractility (EF, systolic times, TDI velocities MV and TV anullus, VTI-LVOT
-Assess and grade MR and TR, evaluate PH
-Look for SAM and dynamic LVOTO

Fluid responsiveness
-Static measures: IVC diameter and CI, LV and RV dimensions and morphology
-Dynamic measures (VTI-LVOT variations during respiration or PLG, in ventilated patients (>12% variation of VTI-LVOT)

Adequacy and monitoring of MCS
-Search for contraindications (aortic regurgitation, PFO, thrombus)
-Guide device and cannula placement
-Evaluate for efficacy of support and unloading
-Search for complications (cannula migration, no AV opening, aortic root thrombosis, LV distension, retrograde systolic PVF)
-Guide MCS weaning: assess dynamic changes of Echo parameters during reduction of support (improving LV and RV contractility, VTI-LVOT>10cm, AV opening)

**ideally an immediate, comprehensive study undertaken by an expert in TTE and TEE should be performed*

Level III
Non-PCI capable centers

Level III
Non-PCI capable centers

Level II

PCI capable centers

PCI facilities 24/7

Level III
Non-PCI capable centers

Level II

PCI capable centers

PCI facilities 24/7

Level I

CS centers (core centers)

hemodynamics and PCI facilities 24/7
advanced MCSs available 24 /7
on-site cardiothoracic surgery
multidisciplinary "CS team"

High volume centers
Nurse/patient ratio 1:1

- Cardiac surgery
- LVAD/biVAD
- Transplant
- Palliative care

Mobile ECMO Team

Level III
Non-PCI capable centers

Level III
Non-PCI capable centers

Level II

PCI capable centers

PCI facilities 24/7

Home/Satellite Centre

Ambulance
Oxygen administration
Peripheral vein catheter
Fluid infusion
ECG suggesting MI-Aspirin

Emergency Department
O^2 or Ventilatory support
Hemodynamic instability: NE or/and Dob; if CA, continues IMV and ECMO
12 leads ECG and Echocardiography (**I/C**)

AMI related CS

Emergency Coronary Angiography

No Mechanical Complications

Suitable for PCI
Emergency PCI on culprit vessel (**I/B**)

Not Suitable for PCI
Emergency CABG (**I/B**)

RV infarction
Revascularization
Avoid fluid overload
NE if low SBP

Mechanical Complications

Heart Team:
Type/Timing of intervention
Need of IABP (**IIa/C**) or other MCSs

VSR
Surgery/Interventional +/-CABG (**I/C**)

Wall rupture
Pericardiocentesis
Surgery +/-CABG (**I/C**)

Acute MR
MV Surgery +/-CABG (**I/C**)

Not AMI related CS

Identify etiology: Cardiomyopathies, Tamponade, Valvular Diseases, Myocarditis, RV failure, post cardiac surgery CS, Takotsubo, Cancers

Etiological treatment

Activation of **Heart Team** for:
-Short term MCSs (**IIb/C**)
-Urgent surgery: Tamponade, NV/PV endocarditis, PCS-CS

ICU/ICCU: monitoring, volume optimization, inotropes/vasopressors, organ function management

If severe hemodynamic instability or refractory CS : ***temporary percutaneous MCSs*** (**IIb/ C**)

improving

Weaning of temporary MCSs

GDMTs in HFrEF patients
Continue etiological treatment
Assessment pre-discharge

Not improving

Heart Team:
Age, neurologic deficit, bleeding, comorbidities, RV function

Long-term surgical MCS (LVAD)
Destination therapy Bridge to recovery Bridge to transplant

Palliative care